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Health and Environmental Effects  
Profile for Mephosfolan

(U.S.) Environmental Protection Agency  
Cincinnati, OH

Jan 84



U.S. Department of Commerce  
National Technical Information Service

**NTIS**

HEALTH AND ENVIRONMENTAL EFFECTS PROFILE  
FOR MEPHOSFOLAN

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE  
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT  
OFFICE OF RESEARCH AND DEVELOPMENT  
U.S. ENVIRONMENTAL PROTECTION AGENCY  
CINCINNATI, OH 45268

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| 16. ABSTRACT<br><p>The Health and Environmental Effects Profile for <u>mephosfolan</u> was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.</p> <p>Quantitative estimates have been presented provided sufficient data are available. <u>Mephosfolan</u> has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for <u>mephosfolan</u> is <math>9 \times 10^{-5}</math> (mg/kg bw/day) for oral exposure.</p> <p><i>9 to the minus 5 power</i></p> |                                                  |                                                       |
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# DISCLAIMER

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## PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEP's are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or  $q_1^*$  is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEP's will become part of the EPA RCRA docket.

#### ACKNOWLEDGEMENTS

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# LIST OF ABBREVIATIONS

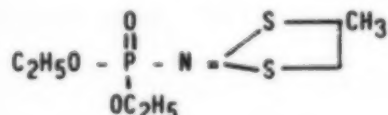
|                  |                                  |
|------------------|----------------------------------|
| bw               | Body weight                      |
| LD <sub>50</sub> | Dose lethal to 50% of recipients |
| MS               | Mass spectrometry                |
| ppm              | Parts per million                |
| TLC              | Thin-layer chromatography        |
| TLV              | Threshold limit value            |

## 1. INTRODUCTION

### 1.1. STRUCTURE AND CAS NUMBER

Mephosfolan is the common name for phosphoramidic acid, (4-methyl-1,3-dithiolan-2-ylidene)-, diethyl ester, formerly known as imidocarbonic acid, phosphonodithio-, cyclic propylene P,P-diethyl ester (U.S. EPA/NIH, 1983). This chemical is also known as 1,3-dithiolane, 2-(diethoxyphosphinylimino)-4-methyl-; cyclic propylene (diethoxyphosphinyl)dithiolimidocarbonate, among others (NIOSH, 1983). Mephosfolan was introduced under the code number E1 47,470 and the trade name Cytrolane, by the American Cyanamid Company in 1963 (BCPC, 1977).

Mephosfolan has the following structure:



Molecular formula:  $C_8H_{16}NO_3PS_2$

Molecular weight: 269.3

The Chemical Abstracts Service (CAS) Registry number for mephosfolan is 950-10-7.

### 1.2. CHEMICAL AND PHYSICAL PROPERTIES

Mephosfolan is a yellow to amber liquid with the following properties (BCPC, 1977).

|                |                                                                                           |
|----------------|-------------------------------------------------------------------------------------------|
| Boiling point: | 120°C at $1 \times 10^{-3}$ mm Hg                                                         |
| Density:       | 1.539 at 26°C                                                                             |
| Solubility:    | moderately soluble in water; soluble in acetone, ethanol, ethylene dichloride and benzene |
| Stability:     | stable in water at neutral pH, but hydrolyzed at pH <2 and >9.                            |

### 1.3 PRODUCTION DATA

Mephosfolan was produced by the American Cyanamid, Co., Linden, NJ and Bofors Nobel, Inc. and Lakeway, Inc., Muskegon, MI (USITC, 1981); there is no indication that the insecticide is under current production, however, since it is not listed in the 1982 or 1983 editions of the Directory of Chemical Producers (SRI, 1982; 1983). According to the Chemical Economics Handbook (Ayers and Johnson, 1976), the American Cyanamid Co. manufactured 1 million pounds/year as of 1976 (see Appendix for literature searched; also additional classified information is available. See Chapter 8 for a more complete explanation).

Mephosfolan is synthesized by reacting 2-imino-4-methyl-1,3-dithiolan with diethyl phosphorochloridate (BCPC, 1977).

### 1.4. USE DATA

This chemical has been used as an insecticide to control stem borers, bollworms, whiteflies, mites and aphids on rice, maize, cotton, sorghum, sugarcane, vegetables and fruit (BCPC, 1977; Ouellette and King, 1977).

## 2. ENVIRONMENTAL FATE AND TRANSPORT

Information on the fate and transport of mephosfolan in the environment is limited. As an insecticide used to control pests on crops, mephosfolan enters the soil by direct application to fields. The fate of the chemical in soil will depend upon its ability to be hydrolyzed or photodegraded (at the soil surface) or to be biodegraded by soil microorganisms.

Mephosfolan is likely to be stable to hydrolysis under field conditions since it hydrolyzes readily only at  $2 < \text{pH} < 9$  (BCPC, 1977). As discussed below, photodegradation in water occurred readily (Ku et al., 1979) and may also occur at the soil surface. Information regarding microbial degradation in soil was unavailable.

Ku et al. (1978) studied the fate of  $^{14}\text{C}$ -mephosfolan, labeled in the imidocarbonate carbon atom, in simulated rice paddies composed of silt loam soil (pH 6.2) in polyethylene tanks, rice seedlings, water and goldfish. After harvest of the rice plants (19 weeks after treatment with mephosfolan at a rate of  $14 \text{ mg}/2 \text{ ft}^2$ ), 20.3% of the radioactivity remained in the soil; 15.3% was methanol extractable and consisted solely of unchanged mephosfolan. The remaining 5% of radioactivity represented degradation products, although no information on the mechanism of degradation was provided.

Transport of mephosfolan in soil will be governed by the degree to which it evaporates into air or leaches into groundwater. Information on the volatility of the chemical was unavailable. In the previously described simulated rice paddy ecosystem (Ku et al., 1978), 13.9% of the applied radioactivity from  $^{14}\text{C}$ -mephosfolan remained in the top 5 inches of the 10-inch deep soil, while 6.4% leached into the lower 5 inches, 19 weeks after application of the chemical. In an abstract of a study by Sahu and

Agnihotri (1981), it was reported that mephosfolan leached rapidly into a 15 cm depth of soil in which growing plants had been treated at a rate of 1.0 kg/ha, and persisted for 75 days. Residues in the top 0.15 cm of the soil persisted for 60 days. It was not stated in the abstract what percentage of residues were detected in the soil levels or at what rate leaching occurred.

Mephosfolan can enter the aquatic environment by leaching into groundwater or in runoff following precipitation. The fate of mephosfolan in water will depend on its ability to be hydrolyzed, to undergo chemical and photochemical reactions or to be microbially degraded. As previously discussed, hydrolysis is unlikely. Ku et al. (1979) reported the half-times for the first order photodegradation of 100 ppm  $^{14}\text{C}$ -mephosfolan in distilled water, in 2% acetone-water and in natural paddy water irradiated by sunlight to be 18, 7 and 14 days, respectively. After 5 weeks of exposure to sunlight, ~26, 4 and 19%, respectively, of the parent compound remained. Only ~10% of the original mephosfolan disappeared from dark-control paddy water at 5 weeks, indicating a minor role of microbial degradation. Comparison of the rates and degrees of photodegradation in paddy water and in distilled water with that of acetone-photosensitized degradation indicated that paddy water contained some photosensitizing component. The photolysis products were similar for all three systems and were identified as diethyl methylphosphate, cyclic S,S-propylene dithiocarbonate, 5-methyl-2-imino-1,3-dithiolane, phosphoric acid, ethyl phosphate and diethyl phosphate. Only unchanged mephosfolan, however, was found in the paddy water in the simulated ecosystem (Ku et al., 1978), but much of the radioactivity had been removed by uptake by the growing rice plants.

The only other information available on the removal of mephosfolan from water was obtained from data of uptake by goldfish in the previously

described rice paddy ecosystem (Ku et al., 1978). The bioaccumulation constant (total  $^{14}\text{C}$  concentration in the fish/total  $^{14}\text{C}$  concentration in water) was 8.5 and the ecological magnification constant (total parent mephosfolan concentration in fish/total parent mephosfolan concentration in water) was 0.56, indicating a very low tendency for the chemical to bioaccumulate.

Pertinent data regarding the fate and transport of mephosfolan in the atmosphere were not located in the available literature (see Appendix for literature searched; also additional classified information is available. See Chapter 8 for a more complete explanation).

### 3. EXPOSURE

Pertinent data regarding monitoring for and exposure to mephosfolan were not located in STORET or in any other source.

## 4. PHARMACOKINETICS

### 4.1. ABSORPTION

Only one abstract was located that dealt with the absorption, of mephosfolan in mammalian species. Bakry and Abou-Donia (1981) administered a single oral dose of 2 mg [ $^{14}\text{C}$ ]mephosfolan labeled in the imido carbon (0,0-diethyl-4-methyl-1,3-dithiolan-2-ylidenephosphoro[ $^{14}\text{C}$ ]amaldite)/kg bw to female mice (strain unspecified) on day 17 of gestation. Based on distribution and excretion data (see Sections 4.2. and 4.4.), absorption from the gastrointestinal tract was rapid; however, the rate of absorption was not reported.

### 4.2. DISTRIBUTION

In the only available distribution study, Bakry and Abou-Donia (1981) found high, but unspecified,  $^{14}\text{C}$  concentrations in the liver, skin, blood and fetus within 30 minutes after oral administration of 2 mg [ $^{14}\text{C}$ ]mephosfolan/kg bw to female mice. Total body levels decreased slowly, with a half-life of 17.6 hours. Radioactivity reached peak levels of 3.9% of the dose in the fetuses at 1 hour and was eliminated at a rate substantially slower than from the maternal animal ( $t_{1/2} = 108.2$  hours).

### 4.3. METABOLISM

The metabolism of mephosfolan has also been studied by Ku and Kapoor (1981). [ $^{14}\text{C}$ ]Mephosfolan labeled in the imido carbon was administered to rats (route and strain unspecified) and the urine was analyzed by TLC and MS. The authors found that the major routes of metabolism involved either oxidation of the methyl group on the dithiolane ring, resulting in the formation of a carboxylate ion, or hydrolysis of the P-N bond, resulting in ring-opening and release of the thiocyanate ion. The major tissue metabolite (tissue unspecified) was found to be the thiocyanate ion.

#### 4.4. ELIMINATION

The only study in the available literature that deals with the excretion of mephosfolan is that of Bakry and Abou-Donia (1981). Female mice were given a single oral dose of 2 mg [ $^{14}\text{C}$ ]mephosfolan/kg bw. The major route of excretion was urinary, accounting for 36.6% of the dose within 24 hours. Expired air also contained significant amounts of radioactivity (4.05% of the total dose), but only 0.77% of the dose was eliminated in the feces. TLC and MS analysis indicated that most of the radioactivity recovered in the feces, urine and tissues was in the form of unidentified polar metabolites.

## 5. EFFECTS

### 5.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of mephosfolan were not located in the available literature. It is not scheduled for testing by the National Toxicology Program Carcinogenesis Testing Program (NTP, 1983).

### 5.2. MUTAGENICITY

Jeang and Li (1980) tested 80 pesticides, including mephosfolan, in the Ames assay, both with and without activation by S9 mix. Mephosfolan (concentrations unspecified) was not reported to be mutagenic under these conditions. No details of the study were presented, hence the study is judged to be inadequate for evaluation.

### 5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of mephosfolan were not located in the available literature.

### 5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of mephosfolan were not located in the available literature.

### 5.5. CHRONIC AND SUBCHRONIC TOXICITY

Pertinent data regarding the chronic and subchronic effects of mephosfolan to mammalian species were not located in the available literature (see Appendix for literature searched; also additional classified information is available. See Chapter 8 for a more complete explanation).

### 5.6. OTHER RELEVANT INFORMATION

Oral LD<sub>50</sub>s have been reported for rats (9 mg/kg bw) and mice (11 mg/kg bw), and a dermal LD<sub>50</sub> of 9.7 mg/kg bw has been reported in rabbits (NIOSH, 1983).

Abou-Donia et al. (1974) have investigated the induction of delayed neuro-toxicity in chickens. When the LD<sub>50</sub> (2.8 mg/kg bw) was administered to 10 birds, no delayed neurotoxic symptoms were detected in any of the surviving birds within 2 months of dosing.

## 6. AQUATIC TOXICITY

Pertinent data regarding the toxicity of mephosfolan on aquatic organisms were not located in the available literature.

## **7. EXISTING GUIDELINES AND STANDARDS**

### **7.1. HUMAN**

The American Conference of Governmental Industrial Hygienists has not established a TLV for mephosfolan (ACGIH, 1980, 1982). No existing guidelines or standards were located in the available literature.

### **7.2. AQUATIC**

Guidelines and standards for the protection of aquatic organism from the toxic effects of mephosfolan were not located in the available literature.

## 8. RISK ASSESSMENT

Only limited data regarding the toxicity of mephosfolan were located in the available literature. No pertinent information regarding the carcinogenicity of mephosfolan was located. Abou-Donia et al. (1974) reported that mephosfolan does not induce delayed neurotoxicity in chickens. The only other toxicity data available were acute oral LD<sub>50</sub> values of 9 mg/kg bw for rats and 11 mg/kg bw for mice, and an acute dermal LD<sub>50</sub> value of 9.7 mg/kg bw for rabbits (NIOSH, 1983). It was concluded that these data were insufficient for the derivation of a q<sub>1</sub>\* or an ADI.

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment can, however, be presented in this chapter.

The CBI Appendix to this document reviews other animal data from which an ADI was derived. Based on a NOEL of 1.25 ppm mephosfolan in the diet (equivalent to 0.09 mg/kg bw/day based on data on food consumption and weight gain) of rats for 17 weeks and using an uncertainty factor of 1000 (a factor of 10 to convert from subchronic to chronic exposure, a factor of 10 for interspecies extrapolation and a final factor of 10 to protect unusually sensitive members of the human population), an ADI of 0.09 µg/kg bw/day or 6.3 µg/day for a 70 kg man is recommended. At the next highest dietary level, which was started at 5 ppm and progressively increased to 30 ppm over 84 days, liver and kidney weights were reduced and plasma, erythrocyte and brain cholinesterase activities were inhibited.

## 9. REFERENCES

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SRI (Stanford Research Institute). 1983. Directory of Chemical Producers. United States of America. SRI, Menlo Park, CA.

U.S. EPA/NIH. 1983. SANSS (Structure and Nomenclature Search System). Searched through CIS online; July, 1983.

USITC (United States International Trade Commission). 1981. Synthetic Organic Chemicals. United States Production and Sales. USITC. U.S. Government Printing Office. USITC Publication 1292.

## APPENDIX: LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)  
TOXLINE  
MEDLINE  
RTECS  
SCI SEARCH  
OHM TADS  
STORET  
SRC Environmental Fate Data Bases  
SANSS  
AQUIRE

These searches were conducted in July and August, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. TLVs: Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981). Cincinnati, OH. p. 486.

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